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14. ABSTRACT The Advanced Cancer Detection Center has focused on the development and application of new technologies to enhance clinical research. The project has been successful in developing and implementing a variety of leading edge technologies during the past grant period. Employing state of the art informatics, the project has develop a web-based infrastructure that is generalizable and now supports multiple federally supported clinical research initiatives. With an initial focus on cancer detection, the project has expanded to apply lessons learned into a number of differing clinical disorders, including many that are now funded by the DoD under parallel initiatives. Although this represents the final report on this project, the technology that has now been developed has been successfully transitioned to these new projects and its continued success assured.					
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INTRODUCTION:

The **Advanced Cancer Detection Center** (ACDC) of the H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida received initial funding in October 1997. (DAMD17-98-1-8659) In 2001, funding that was appropriated in FY00 and FY01 was awarded separately to the University of South Florida for the project period 2001-2006. (DAMD17-01-2-0056). This report details progress since the 2007 annual report and serves as the final report for this project.

Over the years of this grant cycle, the ACDC has supported a number of basic science, clinical research and clinical translational research projects. The ACDC at the H. Lee Moffitt Cancer Center and Research Institute has addressed the goals identified in its appropriations language through studies that target the discovery of molecular and genetic markers of cancer risk, the identification of individuals at high risk for cancer through screening, and the testing of methods to prevent cancer. In addition, the ACDC created and supported education programs to provide increased cancer awareness, provide screening services, and has established working collaborations with the nearby James A. Haley VA Medical Center, the Bay Pines VA Medical Center and the MacDill Air Force Base Hospital. With the success of the Moffitt Cancer Network in providing online cancer education, that project was expanded to enhance educational and clinical translational research building upon new and emerging technologies.

In order to accomplish these goals, the Advanced Cancer Detection Center has supported research and demonstration projects that further its mission. Each project supported by the ACDC is reviewed for scientific merit by an internal peer group and an external scientific advisory committee. Preference is given to projects that have potential to lead to independent peer reviewed funding. Projects supported during the fiscal years include:

*Epoxide hydrolase genetic polymorphisms and their functional significance,
Automated Quantified Screening for Melanoma,
Breast Cancer Screening in High-Risk Women: Comparison of magnetic resonance
imaging (MRI) with mammography, and
Adaptive Computer Assisted Diagnosis (CAD) Method for Lung Nodule Early Detection.
Development of the Moffitt Cancer Network and
The Tampa Bay Ovarian Cancer Study*

Progress on these studies, including publications have been included in earlier reports.

Since 2006, the project was granted a no cost extension based upon the following continuing activities:

- Develop and implement Pediatric Internet Telemedicine Homecare study to assess efficacy of low bandwidth monitoring, management and treatment in the care of childhood cancer and chronic diseases.
- Develop and implement proof of concept study for genetic counseling delivered from a distance via telemedicine in a multi-center environment.

- Develop and implement an interactive intelligence search and representation system for mining disease information to aid in proper diagnosis.
- Upgrade existing hardware and server environment to replace aging equipment and maintain a state-of-the-art data and informatics infrastructure.

Progress on all these activities were reported in last years annual report. For 2008, the project has been focused on the following tasks, which is detailed in the material to follow:

- **Task 1.** Continue development and application of new technologies for patient reported outcomes and effective mechanisms to enhance patient-provider communication.
- **Task 2.** Develop and implement proof of concept study for genetic counseling delivered from a distance via telemedicine in a multi-center environment.
- **Task 3.** Provide for orderly phase out of ACDC projects and activities and transitioning to other mechanisms for continued support.

BODY:

Overview:

The Advanced Cancer Detection Center has become a significant component of the infrastructure in that it provides a stimulus for research development and promotes inter and intra programmatic collaborations. The Advanced Cancer Detection Center supports pilot studies that can and has lead to peer-reviewed extramural funding.

The ACDC has addressed the goals identified in its appropriations language through studies that target the discovery of molecular and genetic markers of cancer risk, the identification of individuals at high risk for cancer through screening, and the testing of methods to prevent cancer. In addition, the ACDC created a technology base that provides online video streaming, video supported web casting and teleconferencing and the development and application of expert systems. The success of these efforts has led to advances in cancer detection (publications) and the development of systems that have attracted additional peer-reviewed funding. The ACDC has received supplemental funding for a conference on molecular oncology and biomarkers which has been accomplished and a report detailing this activity has previously been submitted.

Recognizing the great success of this effort, the clinical focus of the Advanced Cancer Detection Center has transitioned to other funding sources, most notably the Community Clinical Oncology Program Research Base (described below). The Moffitt CCOP Research Base develops studies focused upon symptom management and quality of life. It is an appropriate successor to the ACDC in that it has continuing peer-reviewed funding from the National Cancer Institute and incorporates a multi-tiered review process that includes both the CCOP Research Base investigators and a review by the National Cancer Institute.

The no cost extension to the final year of the project has allowed the ACDC to pursue primarily advanced technologies and health informatics issues that are necessary to keep the infrastructure relevant to today's technologies and their application. The technology application phase to clinical trials and related studies has been funded with independent grant support from the National Institutes of Health. As well, the telegenetics initiative has resulted in additional technological development to promote its capacity to become a self supporting stand alone project when the ACDC funding ends and new funding opportunities are being pursued.

Since 2007, the Advanced Cancer Detection Center has focused on further development of its Telemedicine and Informatics initiatives as a means to further its education objectives contained in enabling legislation. Those technologies already developed as part of the ongoing Moffitt Cancer Network.

- **Task 1.** Continue development and application of new technologies for patient reported outcomes and effective mechanisms to enhance patient-provider communication.
- **Task 2.** Develop and implement proof of concept study for genetic counseling delivered from a distance via telemedicine in a multi-center environment.
- **Task 3.** Provide for orderly phase out of ACDC projects and activities and transitioning to other mechanisms for continued support.

KEY RESEARCH ACCOMPLISHMENTS:

The material that follows in this section summarizes the key research accomplishments associated with each project and task outlined in the appropriate approved Statement of Work for ACDC approved projects during the 07-08 year. Progress on tasks for previous years have already been reported.

- **Task 1. Continue development and application of new technologies for patient reported outcomes and effective mechanisms to enhance patient-provider communication.**

The research has focused on the development of new platforms for sharing video and audio telecommunication between patients (or study participants) and health care providers emphasizing patient reported outcomes. Earlier technological advances employed interactive voice response systems which have now seen clinical application in projects funded by the National Center for Research Resources:
Interactive Voice Response Diary and Objective Myotonia Measurement as Endpoints for Clinical Trials in Nondystrophic Myotonia, 59th American Academy of Neurology Meeting, Boston, MA, April 28-May 5, 2007.

Interactive voice response diary (IVR) system and quantitative myotonia measurement were evaluated as potential outcome measures for nondystrophic myotonias (NDM) clinical trials

NDM is a heterogeneous group of neuromuscular disorders caused by mutations in skeletal muscle sodium and chloride channels. There are no established treatments for

myotonia despite the availability of agents that deserve careful study. A reliable outcome measure in myotonia is necessary for clinical trials.

Twenty-four subjects enrolled from 6 US, UK, and Canadian sites were categorized as myotonia congenita (MC), paramyotonia congenita (PMC), and other myotonic disorders(OMD). Three possible myotonia measures were assessed: relaxation time following maximum voluntary isometric contraction of the finger flexors (QMA); myotonic discharges on needle EMG, and Interactive Voice Response Diary (IVR), where participants phoned in weekly for 8 weeks to rank severity of stiffness, pain, weakness, and fatigue on a scale of 1-9 and reported frequency in days.

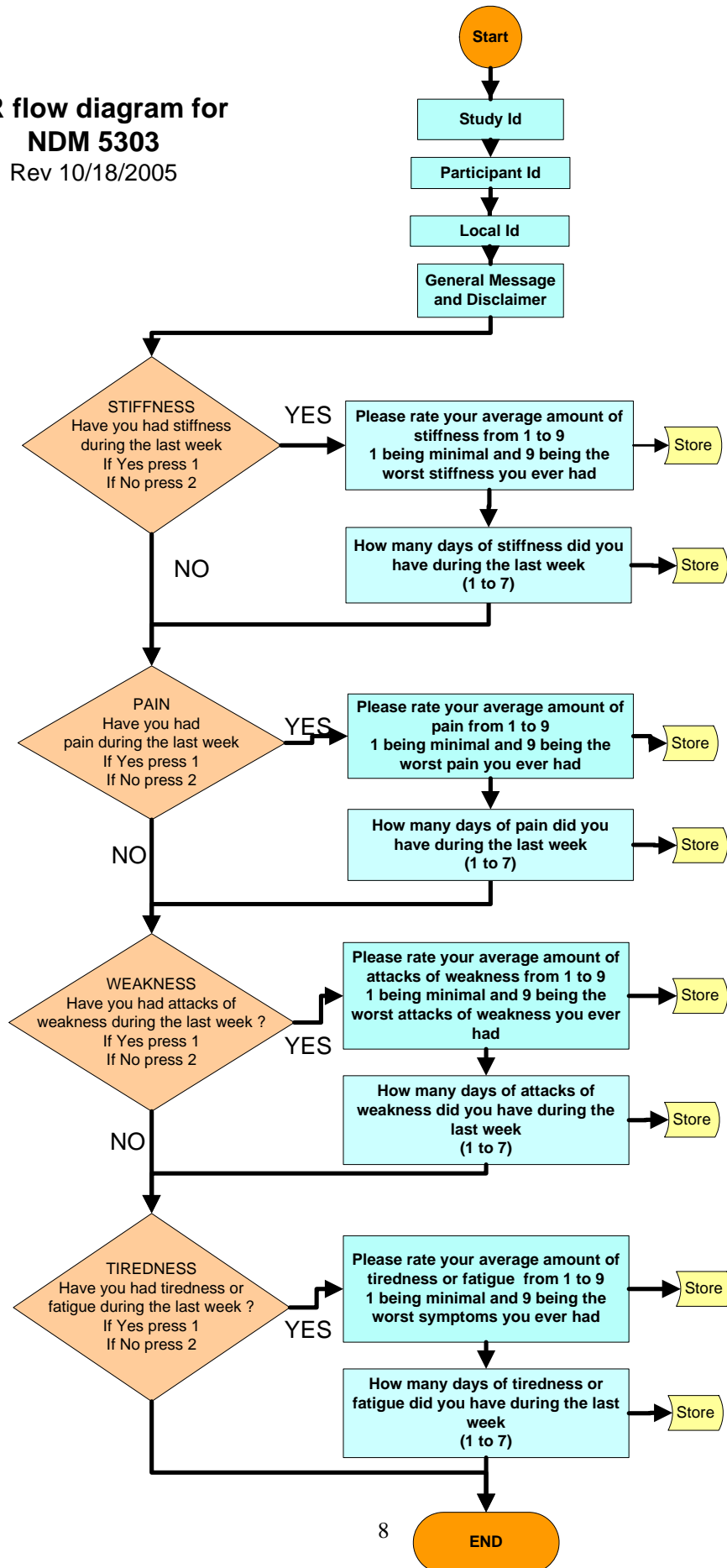
Initial clinical diagnosis: 13MC; 7PMC (4 genetically confirmed); 3OMD. Myotonic discharge potentials were seen in all subjects with no difference in their degree and location among the subtypes. QMA testing showed a delay in relaxation in 4/20 subjects with positive hand grip myotonia. Of the 14/24 subjects who phoned weekly for more than 6 weeks the IVR data showed frequency for the population was stiffness in 97%, pain 63%, weakness 50%, and fatigue 65%. The severity by symptoms was stiffness 4.09 ± 0.42 ; pain 2.34 ± 0.28 ; weakness 2.16 ± 0.39 ; fatigue 2.74 ± 0.41 . The average number of days per week participants experienced symptoms was stiffness 5.01, pain 3.27, weakness 2.12, and fatigue 2.94.

The IVR data showed consistency in self-rated clinical symptoms related to myotonia, making this a potentially useful endpoint for future clinical trials. Quantitative myotonia measure is a less sensitive outcome measure since only a minority showed abnormal results.

The IVR system implemented a structured algorithm for utilizing key pad data collection from touch tone phones for study related data capture tasks. The above abstracts describes the automated implementation of the following algorithm:

IVR flow diagram for NDM 5303

Rev 10/18/2005



The IVR technology has been very successful, well accepted and robust in its application technology for patient reported outcomes. The technology that makes this possible is a PC card that accepts tone-dial (push-button) sounds and can playback pre-recorded (or synthesized) speech in response. The system consists of computer controlled voice and telephone hardware, and custom software. The software includes an application toolkit to facilitate programming of the user applications. The toolkit consists of a device driver (a terminate and stay resident program module) necessary to communicate with the hardware board, and a library of routines. The system is designed to operate continuously and unattended. To ensure security of the system, registration data, and patient reported outcomes, several techniques are employed. They include a log-in procedure, authentication, and maintenance of a register of all telephone calls. Only after authenticating the accuracy of the caller identification number and the study does the system allow the caller to proceed with the data reporting. The system is fully integrated into our Oracle database which allows two way communication and integration with clinical data as appropriate.

The IVR technology has become the cornerstone of new research endeavors and projects. The ACDC has pursued the extension of this technology investigating the utilization of cell phone technology for patient reported outcomes.

The cell phone platform offers several advantages over the IVR system that we sought to exploit. Among them is the use of the screen geography to allow visual scales of severity. As well, since video capture is becoming ubiquitous, this platform allows for the capture of digital images and videos as indicators of patient health care status. An example of the implementation of the same IVR algorithm described above on the cell phone platform is as follows:



For each question, the participant selects the answer by using the left and right arrow keys and then pressing the Choose button. The next question is shown subsequently.



Qualitative scale data is collected by using the left and right arrow keys to move the indicator. This data is then internally transformed to a quantitative scale measure for transmission.



Numeric responses can be entered directly or can be selected from a list of predefined responses.

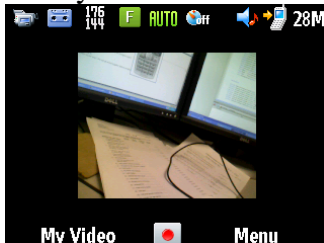


After all questions have been answered a Thank You message is shown. The user presses OK to close the application. The form data is sent automatically via text message with no further action required from the patient.

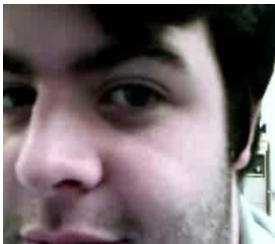
A video application is also relatively easy to implement as well.



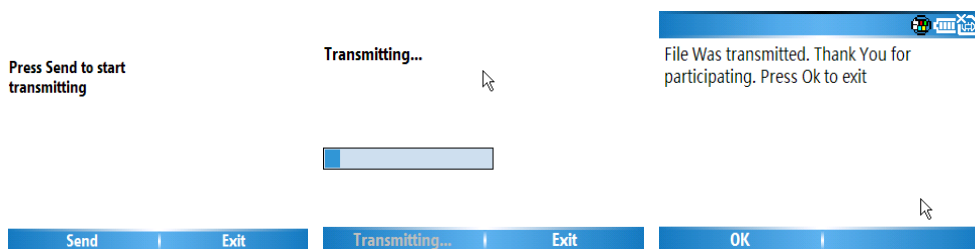
The system can use the standard video interface of the telephone.



This is an example of the standard video interface of a typical cell phone. Video controls are whatever the phone typically uses. An appropriate subject can then be recorded:



The video resolution is adequate for many clinical applications. While not precise enough for pathological diagnosis, it is sufficient to describe symptoms, or changes in symptoms, in many situations. Our pilot work was been applied to the area of periodic paralysis where characteristic muscle tremors or eye movements can easily be visualized.



A

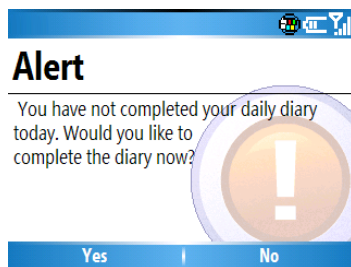
B

C

The application that guides the user through simple steps to transmit the video as panels A-C describe. The video stream is sent through TCP/IP connections using the internet to a web server. The Internet is the preferred method to transfer video. Text data can be sent via an SMS gateway which is very inexpensive.

The application requires Windows Mobile 5 smart phones and universally available cellular service. It can be installed locally on the phone or it can be downloaded or installed using micro SD card distributed by a central site. If it is preloaded on an SD card, the user simply inserts SD class card into the device and the Installer will automatically load. When user is prompted to choose the location of installation, Device (as opposed to SD card) should be chosen.

The application can also be configured to respond to prompts sent out by a central computer. Thus if there is the need to poll individuals to collect data at predefined time periods, the application can respond to prompts which can alert the respondent to complete the needed data form. For example, an alert can be programmed into the system to prompt the data collection step.



Continuing activities after conclusion of the ACDC funding, includes an expanded focus on electronic patient reported outcomes (ePROs) to assess the needs and requirements of patients with different illnesses of varying strengths. Funding from the National Institute of Neurological Diseases and stroke has been successfully obtained.

ePRO needs for reports often include questions regarding the patient's quality of life, pain level, stress level, and comfort level. Traditionally, these reports have been administered through pencil/pen and paper. There are several issues with using a pencil and paper format. A few of them are: patient exhaustion might discourage in-depth answers (where required), handwriting styles, and compliance. In fact, an in-depth paper written by the researcher found, specifically, that "compliance with computerized diaries is often 90% or better, whereas studies have documented only 11% to 20% compliance with paper diaries". Moreover, several studies have been performed which conclude that the efficacy of ePROs is at the very least similar to their pen/paper ancestors, if not better.

With the onset of technology patient reported outcomes are moving to electronic formats; hence there name ePROs (electronic patient reported outcomes). This project has two goals: (1) develop an ePRO web application (web-based mobile pages) that could be delivered from

a server to mobile phones and (2) develop a cell-phone based application that could be downloaded to a user's cell-phone to transmit ePRO answers.

In order to develop the mobile application the following decision tree was provided (Fig 1). The ePRO developed used the decision tree in a (java) **J2ME** based application intended for implementation in cell-phones. J2ME or Java 2 Micro edition is a (much) smaller API intended for use in devices with (sometimes extremely) limited memory. Specifically, J2ME is most often used in cell-phone based applications called **midlets**. See <http://java.sun.com/javame/index.jsp> for more information.

The ePRO midlet consists of four forms (Javax.swing) with one or several questions. There might be more than one question on a page because they share similar attributes which allow them to be presented simultaneously. Longer questions, such as the first are presented on their own page; (1) because they are long and (2) because the user shouldn't have to spend more than 5 seconds (at maximum) scrolling to get from the top of a question to the bottom of the question.

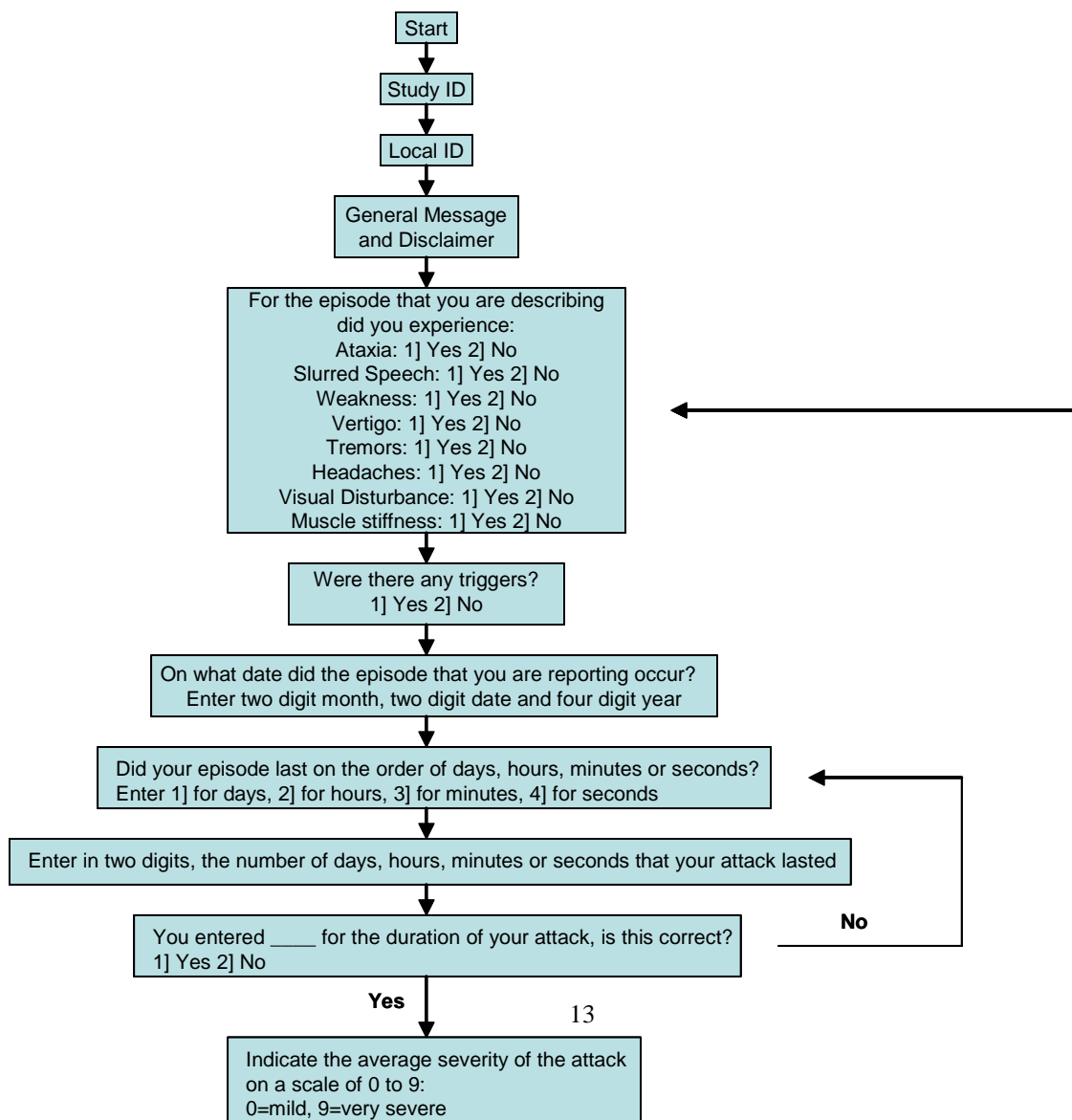




Figure 2



Figure 3

Internally the application rolls to the next page based on the current page's name; in this way there is no counting or need to increment a value (example "page_counter" int).

a) The ones used for this ePRO midlet are described as follows:

Choice Groups:

Each group of questions is a j2me choice group. Choice groups are literally a group of choices which a user can select from. A choice group can be either exclusive (radio button) or multiple (check boxes). For this ePRO the exclusive configuration was chosen since it allows a user to select only yes or only no for yes/no questions or questions which require an exclusive answer. See <http://www.java2s.com/Code/Java/J2ME/multipleChoiceGroup.htm> for more information on Choice Groups.

DateFields:

A date field is self-descriptive. It is simply a field which allows a user to select a date from a navigable calendar. Initially, the first time the user sees a Date field it consists of the word date between two brackets (see Fig 3). Once they click on the <date> selection they are presented with a calendar that allows them to select a year/month/day date (Fig 5). Once they save their date they are returned to the previous screen, with the date field presenting their selection.

Part 2

Were there any triggers?

☒ Yes
☐ No

On what date did the episode that you are reporting occur?

Wed, 15 Oct 2008

Did your episode last on the order of days, minutes, hours or seconds

☒ days
☐ hours
☐ minutes
☐ seconds

Back Menu

Figure 4

On what date did the episode that you are...

◀ 2008 ▶
◀ October ▶

		1	2	3	4
5	6	7	8	9	10
11	12	13	14	15	16
17	18	19	20	21	22
23	24	25	26	27	28
29	30	31			

Back Save

Figure 5

TextField:

Like the aforementioned objects the text field is self-explanatory; it simply allows a user to enter text. For this survey, the text field was used to get the number of days/hours/minutes/seconds that the attack lasted; therefore it consists of two numbers. See Fig 6.

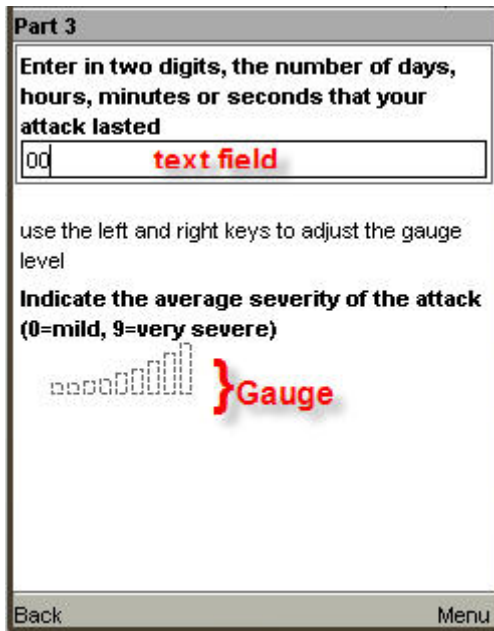


Figure 6

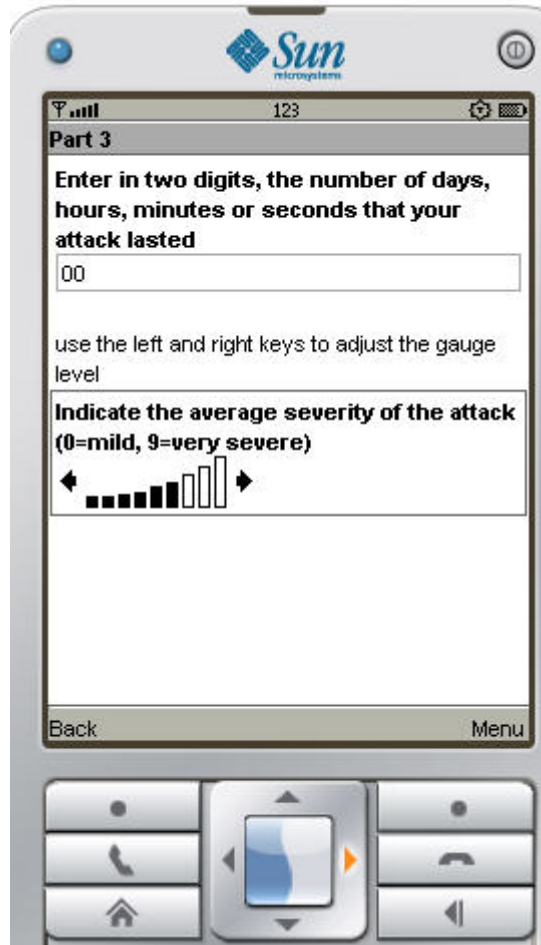


Figure 7

Gauge:

The gauge is an interesting object that allows the user to select a “level”. In this case the level is the “average severity of the attack.” To move the gauge the user simply pushes the left or right arrow on their phone keypad (corresponding to a decrease and increase respectively). See Figure 7.

Part 4

Indicate the effect that this episode had on your daily function. Enter :

☒ 1) Mild=did not interfere with daily activities

☐ 2) Moderate=interfered but did not prevent daily activities

☐ 3) Severe=prevented daily activities

Enter in two digits, the number of episodes like this one which you have just described, that you had in the last 24 hours

Menu

1 **Send**

2 Exit

Back Menu

Figure 8

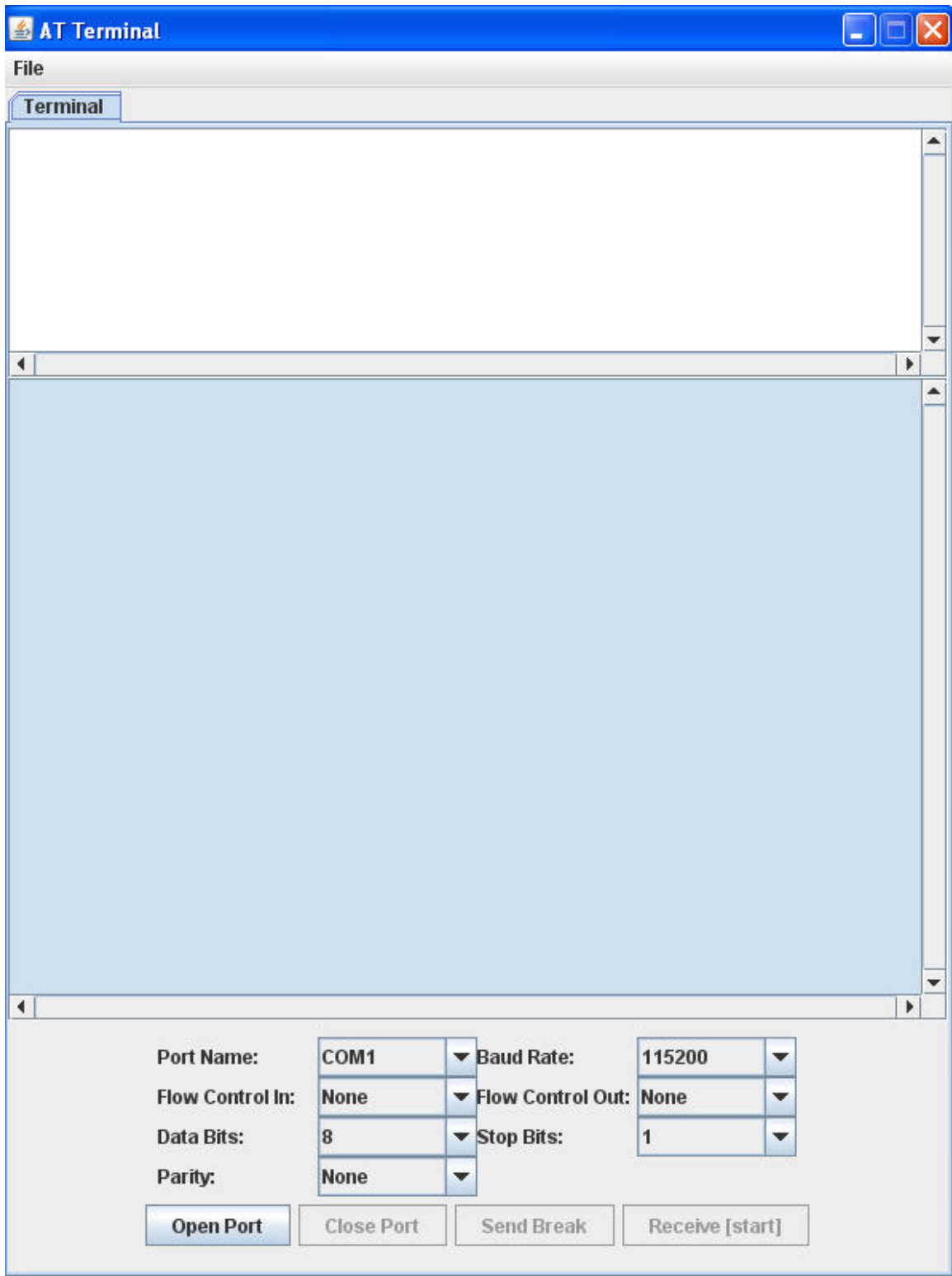
b) Sending the answers

Once the user has finished filling out their form they are presented with a “send option” on the menu bar of the fourth page. This simply allows the user to send their answers to the server. Internally, the application stores the answers as one long comma separated string

I. Receiving the Answers

In order to receive the answers from the ePRO midlet a gsm modem was utilized to accept the sms data. The GSM Modem accepts sms messages sent from a phone and transmits this data through the serial port. In this application, “AT Terminal”, a jar file called javax.comm was needed to interact with the serial port in order to properly receive (and perhaps transmit) data. The GSM modem uses AT Commands to perform actions; AT Commands for the MultiTech Edge Modem can be found here:

<http://www.multitech.com/DOCUMENTS/Collateral/manuals/S000381F.pdf>.



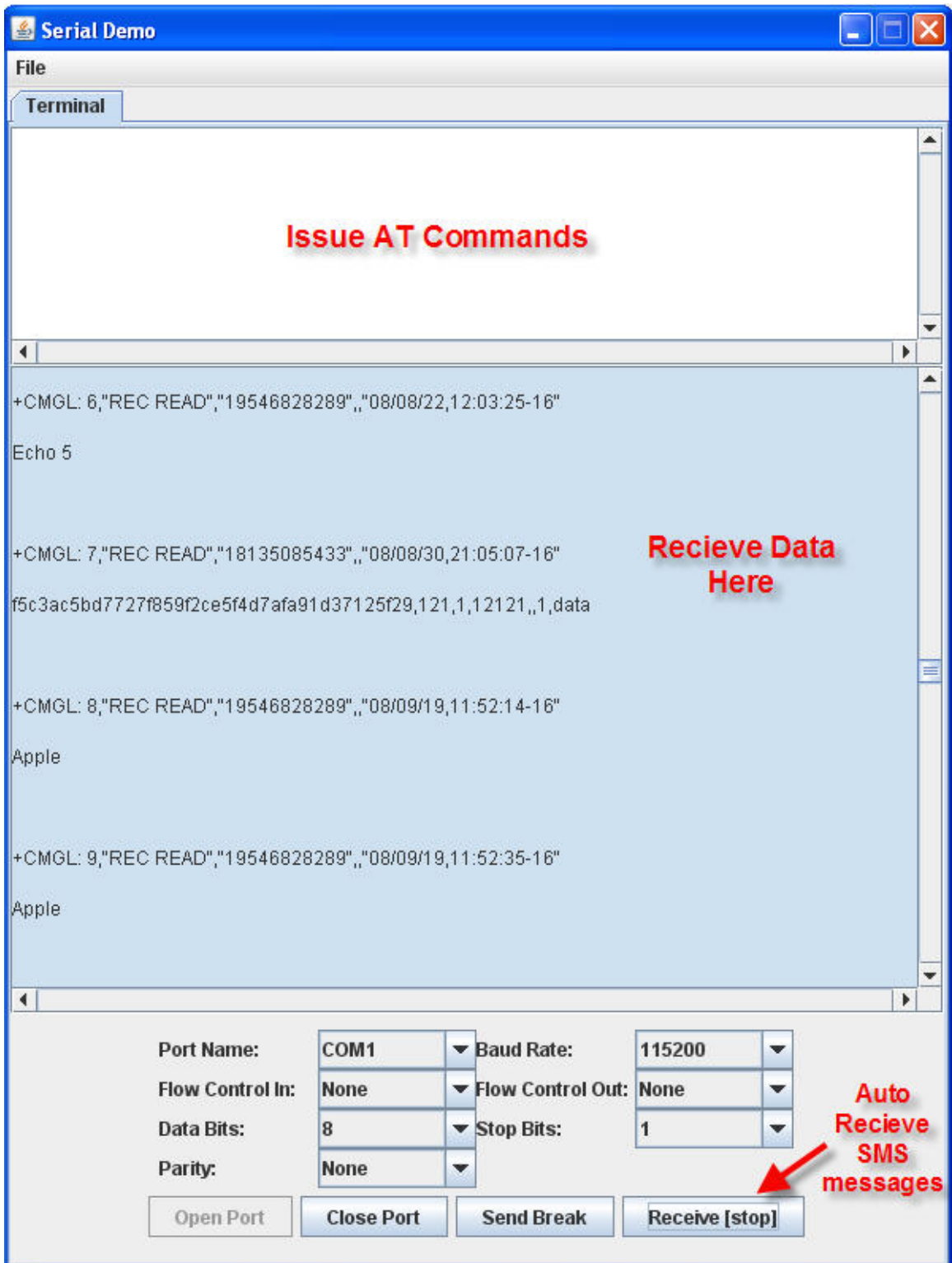


Figure 8 Serial Port Application

Figure 8 shows the “AT Terminal” which receives the sms message through the serial port that the gsm modem is connected to. The button “Receive” starts a thread that issues a series of AT commands sequentially responsible for reading sms messages from the modems memory. The commands are stored in a string array

```
String outputArgs[] = {"at+cmgl=\"ALL\"\\r\\n"};
```

So all that needs to be changed to auto receive a different series of commands is outputArgs[].

If the user wants to use the application like HyperTerminal, Receive must be off, i.e “Receive[start]”.

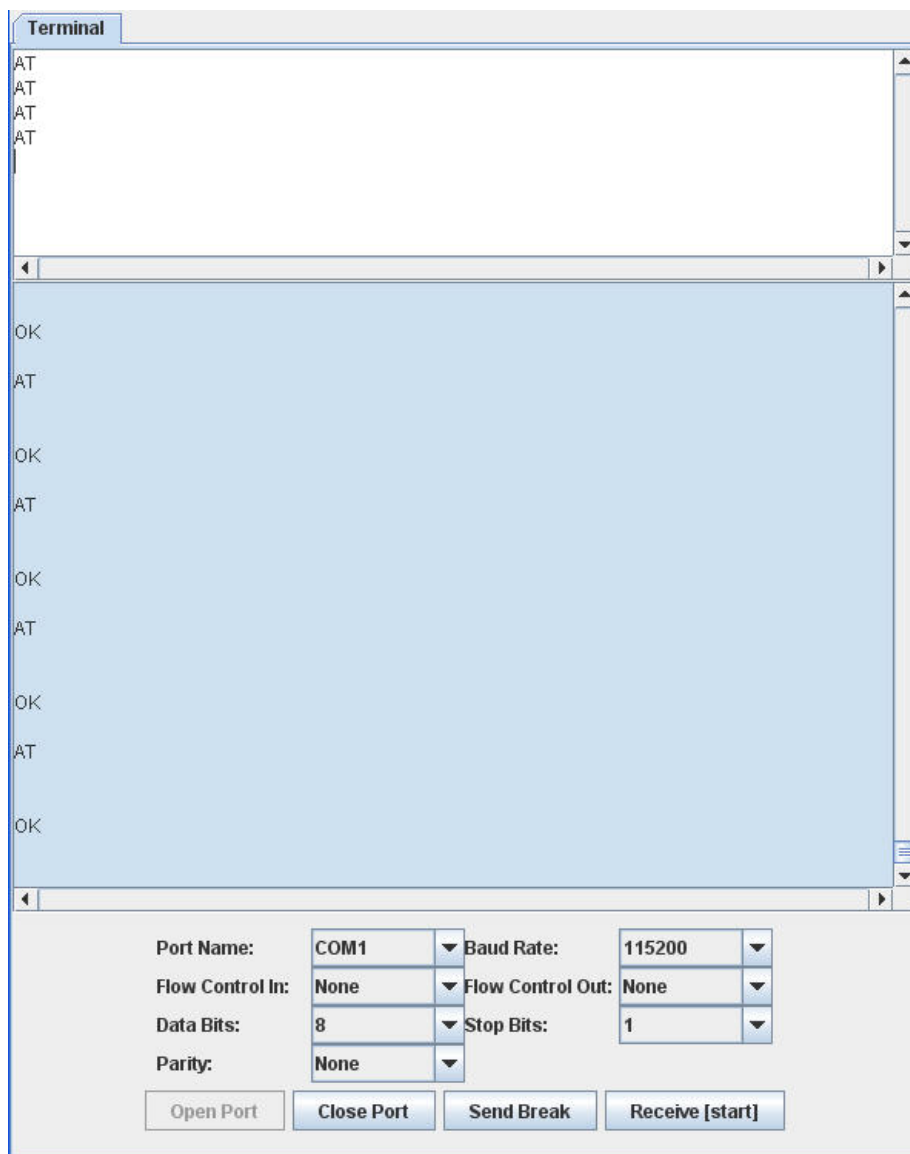
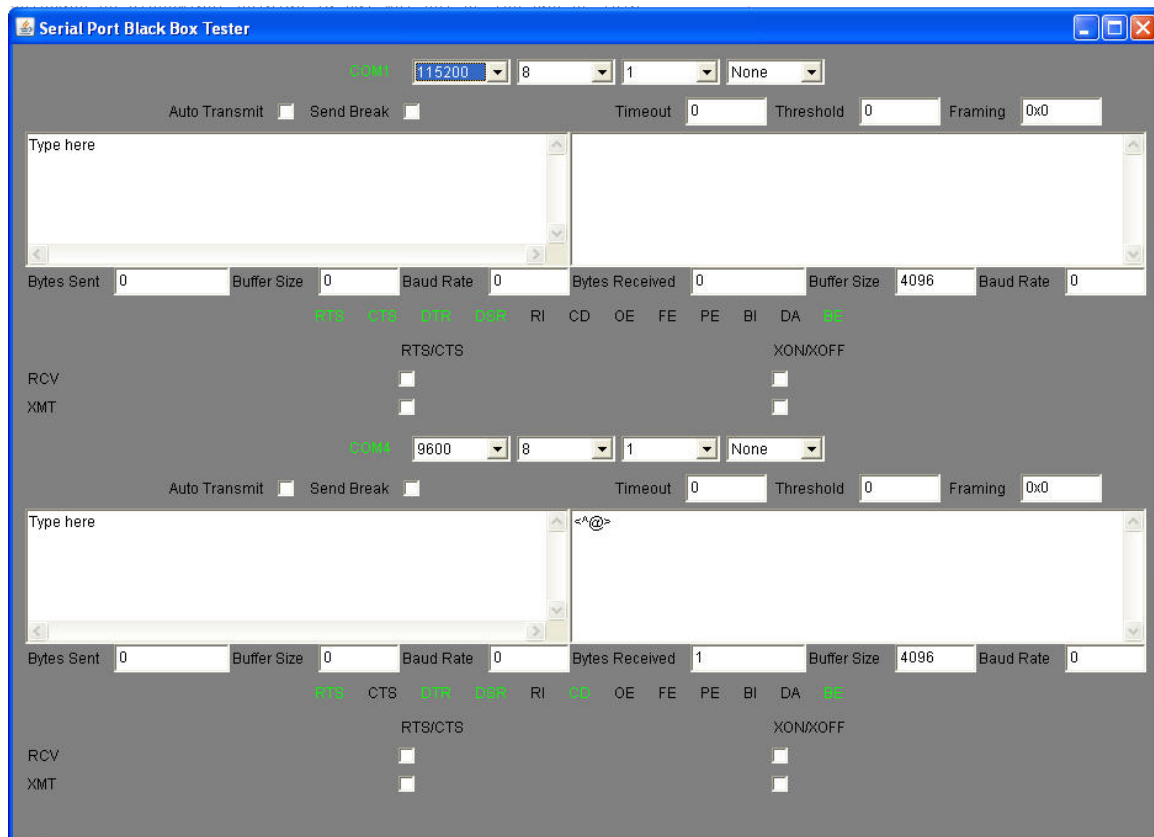


Figure 9 Issuing At Commands

Figure 9 shows how the “AT Terminal” can be used like Windows Terminal to issue AT Commands.

A more detailed application called the “BlackBox” was created which also issues AT Commands but is able to communicate with multiple comm ports; for the server-side component of the e-PRO the application was not used. The code however is commented.



Task 2. Develop and implement proof of concept study for genetic counseling delivered from a distance via telemedicine in a multi-center environment.

In conjunction with the Florida Cancer Genetics Network (FCGN), a network of eleven sites providing genetic counseling throughout the state of Florida, we have implemented a proof of concept study for delivering genetic counseling via telemedicine in a multi-institutional environment. The FCGN formerly based at the Moffitt Cancer Center, has now been transferred to the Division of Epidemiology and Bioinformatics where the ACDC funding is maintained. The FCGN was developed initially under Advanced Cancer Detection Center funding. The Genetics program at the Moffitt Cancer Center recently concluded a proof of concept for genetic counseling via telemedicine that showed promising results. The proof of concept was designed in such a way as to assess the technology as well as the patient and counselor’s resistance to or acceptance of the delivery mode. The patient and counselor were physically located in the same building, although the encounter took place via telemedicine

with the use of audio and videoconferencing software. The FCGN is now a web-based multicenter telegenetics service.

We developed the first internet-based system for cancer genetics risk assessment, genetic counseling and research registry participation. The system automates collection of the family and personal medical history information required for these processes. Data may be 1) entered online or 2) entered on paper forms that can be faxed into a web server for direct (automated) data entry accomplished within minutes. Once entered, data is available for viewing, editing and printing via a secure website. The system generates a family pedigree and risk calculation that can also be viewed or printed from the website. For research initiatives, data in the system can easily be queried to determine the number of individuals available who meet specific eligibility requirements. Authentication and authorization features allow easy access to all data for which the user has permission, while restricting all other data from access. Web access to the system requires a standard web browser (such as Microsoft Internet Explorer version 6.0 or higher) and use of free encryption software available on the internet. The system has two main uses – 1) it automates the data collection, pedigree-drawing and risk assessment procedures of clinical genetic counseling for hereditary cancer susceptibility quickly and easily and 2) it facilitates enrollment of individuals with high cancer risk in a registry designed for individuals who are interested in participating in cancer research studies. The internet-based design of this system makes it accessible to cancer genetics centers around the world.

Our current efforts are to extend the scope of the system to include multiple centers as well to assess efficacy using well defined tools to detect differences in knowledge transfer and patient outcomes relating to overall state of mind post counseling. This extends the current capabilities of the Cancer Network to make scarce resources more widely available to targeted populations and health care providers. The overall goal of the planned work is to implement and measure the performance of a telephonic and web-based delivery system for cancer genetic counseling services. The specific aims of Phase 1 are:

- 1) to expand our prototype telephone-based genetic counseling program to include interactive web-based patient and family histories, automated pedigree development and genetic risk ascertainment to provide a comprehensive system for telephonic delivery of genetic counseling.
- 2) to develop the data collection instruments to assess system performance, including patient surveys, utilizing the expertise of a multidisciplinary advisory board (i.e., clinical geneticists, genetic counselors, physicians, behavioral scientists, health literacy experts, informatics/web systems experts, biostatisticians, health insurance providers/program administrators);

Because this project would require longer term support than available through the ACDC funding mechanism, it was re-defined as an application to the NIH. This application is still pending review.

Task 3. Provide for orderly phase out of ACDC projects and activities and transitioning to other mechanisms for continued support.

All ACDC projects have been transitioned to alternative funding sources. It is noteworthy to comment that all the projects have been independently peer-reviewed and received fundable priority scores at the NIH for continued funding. This is a highly significant accomplishment, attesting to the quality and success of this endeavor. In addition, the infrastructure of the ACDC has been applied to these other projects which has not only been regarded as outstanding, but also can be continued through NIH funding. The basic investment need not be duplicated by the NIH which represents a significant cost savings to the US Government and demonstrates how with the proper planning that these technologies can be generalized to other settings and projects with relatively little incremental cost. The major project funding that now continues is as follows:

Moffitt CCOP Research Base (PI:Krischer)

The H. Lee Moffitt Cancer Center received funding by the NCI in June 2000, and refunded in 2005, to develop a research base as a mechanism for Community Clinical Oncology Programs to access cancer control clinical trials. NCI funded CCOPs, direct affiliates and Moffitt affiliates are eligible to participate in the Moffitt CCOP Research Base. Membership is based on continued funding as an NCI CCOP with satisfactory performance measured by accrual and data quality. The CCOP Research Base provides a technological base for clinical trials that are reviewed, approved and funded by the National Cancer Institute's Division of Cancer Prevention. Thus clinical studies have been transitioned from the ACDC to the NCI in terms of development of new studies, their implementation and evaluation.

The goals of the Moffitt CCOP Research Base are to:

- Develop cancer control trials of high scientific merit for implementation in the community setting.
- Provide community investigators an opportunity to participate in NCI-supported cancer control clinical trials.

The following CCOPs have formal affiliations with the Moffitt CCOP research base:

- Bay Area Tumor Inst. CCOP
- Beaumont CCOP
- Florida Pediatric CCOP
- Cancer Research for the Ozarks CCOP
- Columbus CCOP
- DC United MBCCOP
- LSU – Shreveport MBCCOP
- Medical College of GA MBCCOP
- MeritCare Hospital CCOP
- Nemours – JAX (direct affiliate)
- Northwest CCOP
- Our Lady of Mercy (Direct affiliate)
- San Juan MBCCOP
- Scott & White Hospital CCOP
- So. Texas Pediatric MBCCOP
- Southeast Cancer Control Consortium CCOP

- St. Louis/Cape Girardeau CCOP
- Stroger Hospital of Cook County MBCCOP
- University of Florida – Shands (direct affiliate)

Some clinical studies are the result of pilot development funded by ACDC projects. All are approved by the internal advisory committee and then reviewed and approved by the National Cancer Center before activation. The National Cancer Center, Division of Cancer Prevention provides the scientific review for all clinical studies conducted under this mechanism after review by ACDC leadership and recommendations to support the studies. The studies are monitored by an external data and safety committee and progress is reported annually to the National Cancer Institute. All projects receive IRB review and approval before commencing both at USF and at each participating clinical site. Examples of current studies are:

- Glutamic Acid to Decrease Vincristine Toxicity in Children with Cancer
- Phase II randomized, double-blinded study of an antiemetic pump, using Benadryl®, Ativan® and Decadron® (BAD), for children receiving moderately or highly emetogenic chemotherapy (HLMCC 0503)
- An Open Label Randomized Phase II of an Appetite Stimulant, Cyproheptadine Hydrochloride (*Periactin*®), With and Without a Nutritional Supplement, PediaSure, on Weight in Children with Cancer/Treatment Related Cachexia (HLMCC 0702)
- Prevention of Cancer/Treatment-Related Cachexia in Children Receiving Moderate to Highly Emetic Chemotherapy (HLMCC 0703)
- Modafinil to Improve Neurocognitive Deficits in Children who Received Cancer Treatment Affecting the Central Nervous System (HLMCC 0707)
- Melatonin and sleep hygiene for the treatment of insomnia following cancer therapy in children: A Phase II randomized double blinded cross-over study (HLMCC 0708)
- Risperidone for the Treatment of Cerebellar Mutism Syndrome (HLMCC 0709)
- Stress management therapy for patients undergoing chemotherapy (HLMCC 0501)
- Thyroid function & breast cancer: A pilot study to estimate the prevalence of thyroid dysfunction in women diagnosed with breast cancer and the magnitude of change in thyroid function post-chemotherapy
- The effect of a cysteine-rich whey-derived protein formulation (IMN1207) versus a control protein (casein) on weight, quality of life and survival in patients with advanced non-small cell lung cancer (NSCLC): A phase II study (HLMCC 0801)
- An Open Label Randomized Phase II Study of an appetite stimulant, cyproheptadine hydrochloride, with and without a nutritional supplement, in children with cancer/treatment-related weight loss (HLMCC 0802)
- A randomized, phase II placebo-controlled study of the use of extended-release methylphenidate or modafinil for the treatment of excessive daytime sleepiness in children following cancer therapy (HLMCC 0803)
- A phase II placebo-controlled trial of modafinil to improve neurocognitive deficits in children who received central nervous system targeted therapy for brain tumor treatment (HLMCC 0804)
- A Randomized Placebo Controlled Phase II Study of Lisinopril and Extended – release(ER) Carvedilol Phosphate for the Reduction of Trastuzumab-induced Cardiotoxicity in Breast Cancer Patients Receiving Trastuzumab (HLMCC 0806)

- A Phase II Placebo-Controlled Trial to Determine the Effect of Losartan (Cozaar) on Pulmonary Toxicity in Patients Scheduled to Receive Radiation Therapy for Non-Small Cell Lung Cancer (HLMCC 0704)

Data and Technology Coordinating Center, Rare Diseases Clinical Research Network

To address the challenges inherent in diagnosing and treating rare diseases, the National Institutes of Health (NIH) created the Rare Diseases Clinical Research Network. With \$51 million in grant funding over five years from several NIH components, the network will consist of ten Rare Diseases Clinical Research Centers (RDCRCs) and a Data and Technology Coordinating Center (DTCC). The RDCRCs and the DTCC are located at the following institutions:

- Baylor College of Medicine, Houston, TX - Rare Disease Clinical Research Center for New Therapies and New Diagnostics - Dr. Arthur L. Beaudet
- Boston University School of Medicine, Boston, MA - Vasculitis Clinical Research Network - Dr. Peter A. Merkel
- Children's Hospital Medical Center, Cincinnati, OH - Rare Lung Diseases Clinical Research Network - Dr. Bruce C. Trapnell
- Children's National Medical Center, Washington, DC - Rare Diseases Clinical Research Center for Urea Cycle Disorders - Dr. Mark L. Batshaw
- The Cleveland Clinic Foundation, Cleveland, OH - Bone Marrow Failure Clinical Research Center - Dr. Jaroslaw P. Maciejewski
- University of Rochester, Rochester, NY - Nervous System Channelopathies Pathogenesis and Treatment - Dr. Robert C. Griggs
- The Mount Sinai School of Medicine, New York, NY - The Natural History of Rare Genetic Steroid Disorders - Dr. Maria I. New
- University of Colorado Health Sciences Center, Denver Colorado - Cholestatic Liver Disease Consortium - Dr. Ronald Sokol
- University of North Carolina, Chapel Hill, North Carolina - Genetic Diseases of Mucociliary Clearance Consortium - Dr. Michael Knowles
- Duke University - Rare Thrombotic Disease Clinical Research Consortium - Dr. Thomas Ortel
- University of South Florida and the H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL - The Data and Technology Coordinating Center - Dr. Jeffrey P. Krischer

Approximately 25 million people in the United States are affected by an estimated 6,000 rare diseases or conditions. Diseases to be studied in the centers include: urea cycle disorders; Angelman's syndrome; Prader-Willi syndrome; Rett syndrome; periodic paralysis; non-dystrophic myotonic disorders; episodic ataxia; aplastic anemia; paroxysmal nocturnal hemoglobinuria; single lineage cytopenias, including granular lymphocyte leukemia, pure red cell aplasia, and myelodysplastic syndromes; vasculitis disorders; inborn defects in steroid

hormone pathways; alpha-1 antitrypsin deficiency; lymphangioleiomyomatosis; pulmonary alveolar proteinosis; and hereditary idiopathic pulmonary fibrosis.

With a collaborative approach, the network focuses on identifying biomarkers for disease risk, disease severity and activity, and clinical outcome, while encouraging development of new approaches to the diagnosis, prevention, and treatment of rare diseases.

The network facilitates increased collaboration and data sharing between investigators and patient support groups working to improve the lives of those affected by these diseases and potentially prevent or eliminate these diseases in the future.

This network supports the re-engineering of the clinical research enterprise component presented recently in the "Roadmap for Medical Research" by Dr. Zerhouni, NIH Director. Each research center consists of a consortium of clinical investigators partnering with patient support groups and institutions within and outside of the United States that have agreed to work together studying a group of rare diseases. In addition to fostering collaborative research, the RDCRCs will train new investigators for the represented rare diseases and provide content for a public Web site on rare diseases research.

Integration of various kinds of data including genetic, microarray, clinical, laboratory, and imaging, is one of the goals of this informatics approach to clinical research being pursued at the University of South Florida. The RDCRCs and their sites will work with the DTCC in developing common data elements, data standards, and data structures. The DTCC will incorporate new approaches to data sharing and federated databases at distributed sites that are scaleable or have the potential for future expansion and adaptation. This approach will enable researchers to integrate data with other clinical networks such as the National Electronic Clinical Trials and Research (NECTAR) network.

Each RDCRC utilizes the resources available at the General Clinical Research Centers -- 82 facilities distributed across the United States that provide clinical investigators with specialized research environments and specially trained research personnel. Supported by NCRR, the facilities include nursing staff, research subject advocates, and various core technologies, including sophisticated laboratories, nutrition staff, and imaging facilities.

The Moffitt Cancer Center and Research Institute is one of the clinical sites of the RDCRN through its affiliation with the Bone Marrow Failure Consortium, based at Cleveland Clinic and through its close association with the Data Technology and Coordinating Center. Drs. Alan List and P.K. Burnette, members of the Moffitt Malignant Hematology Program, have been collaborating with Dr. Krischer on several new projects and applications for additional funding. The ACDC Cancer Network web tools and informatics technology has served as the technological underpinnings for this effort. The technology developed through the Moffitt Cancer Network has been extended to build upon the developments supported by the ACDC. For example, the use of low bandwidth video streaming and video conferencing to the desktop, developed under the ACDC funding, has been transformed to provide video libraries for education and training and to permit multi-site videoconferencing for research presentations.

Drs. Rachel Richesson (Informaticist), Larry Hall (Professor of Computer Science) and Jeffrey Krischer all receive support from this funding mechanism which further enhances the technology infrastructure that has been built.

In 2008, an application was made by Dr. Krischer for the continuation of this project and it did extremely well in peer review and will be re-funded for the period 2009-2014.

The Data Coordinating Center for the Study of the Environmental Determinants of Diabetes in the Young. (PI: Jeffrey Krischer, Ph.D.)

The aetiology of type 1 diabetes (T1D) remains unknown, however, a growing body of evidence points to infectious agents and/or components of early childhood diet as triggers of islet autoimmunity and promoters of progression to diabetes. To test these hypotheses, large groups of young children at risk for T1D must be followed prospectively with collection of appropriate samples at frequent intervals. State-of-the-art techniques must be used for sensitive and specific detection of candidate infectious agents and nutritional biomarkers. The National Institutes of Health (NIDDK, NIAID, NICHD & NIEHS), JDRF and CDC have established the TEDDY Study consortium of six Clinical Centres in the U.S. (Colorado, Georgia/Florida and Washington) and Europe (Finland, Germany and Sweden) and a Data Coordinating Centre (Tampa, FL) to identify environmental factors predisposing or protective for islet autoimmunity and T1D.

From 2004-2007, Clinical Centres will screen over 320,000 newborns from both the general population and families already affected by T1D to identify an estimated 13,320 children with high risk HLA-DR/DQ genotypes. Of those, 7,092 (1,152 first degree relatives and 5,940 newborns with no family history of T1D) will be enrolled in prospective follow-up beginning before the age of 4 months. The follow-up visits are scheduled every 3 mo up to 48 mo of age with subsequent visits every six mo until age 15 yr. Blood samples will be taken at each visit; monthly stool samples will be collected for infectious agents. Dietary exposures will be assessed through biomarkers, questionnaires and a diary kept by parents. Psychosocial factors and impact on participating families will be assessed. Primary outcomes include: 1) appearance of one or more islet autoantibodies (IAA, GADA or IA-2A) confirmed at two consecutive visits; 2) development of T1D. By age 15, an estimated 800-1,200 children will develop islet autoimmunity and 400 will progress to T1D. A central repository will preserve biologic samples for future hypothesis-based research.

Based upon competitive application, Dr. Krischer has established a Data Coordinating Center (DCC) for this study using the technology and bioinformatics developed under the ACDC funding. The DCC plays an active role in the development of study protocols and the data management and analysis necessary to support them. Working with the Clinical Centers, the DCC provides expertise regarding alternative study designs to achieve stated objectives. It is conceivable that case-control, case-case and cohort designs may all be considered to address certain objectives in at risk populations. Issues regarding matching and the selection of controls, as well as the logistics of recruitment and retention are all salient to decisions regarding feasible study development, design and implementation. The DCC leads the Consortium Steering Committee and works closely with CC directors to establish the protocol(s) to be followed. The DCC has developed subcontracts for central laboratories and monitor their performance.

This project also underwent competitive renewal in 2008 and was awarded funding until 2017.

The Type 1 Diabetes Trialnet Data Coordinating Center

This project funding is to serve as the TrialNet Coordinating Center (TNCC) for “Type 1 Diabetes TrialNet” (TrialNet) and shall be responsible for design and implementation of clinical trials, observational studies and associated mechanistic studies conducted by a network of Clinical Centers and associated clinical sites, for direction of communication and coordination among the clinical centers and for management of the collection and analysis of genetic, immunologic, pathogenic, clinical and biological data from the clinical sites. The TNCC will also be responsible for: 1) support of study protocols and Manual of Operation for each TrialNet study; 2) maintaining the TrialNet website, and 3) organizing TrialNet Steering Committee meetings, Data Safety Monitoring Board (DSMB) meetings, External Advisory Board (EAB) meetings and workshops. In addition, the TNCC will be responsible for transferring all data and biosamples that are the property of NIDDK to the appropriate NIDDK repositories.

REPORTABLE OUTCOMES:

Manuscripts, abstracts, presentations:

- Moyers S, Richesson R, Krischer J: Trans-Atlantic Data Harmonization in the Classification of Medicines and Dietary Supplements: A Challenge for Epidemiologic Study and Clinical Research. *Int J Med Inform* 77(1):58-67, 2008.
- Kumar NB, Besterman-Dahah K, Kang L, Pow-Sang J, Xu P, Allen K, Riccardi D, Krischer JP: Results of a Randomized Clinical Trial of the Action of Several Doses of Lycopene in Localized Prostate Cancer: Administration Prior to Radical Prostatectomy. *Clin Med* 1-14, 2008.
- Richesson RL, Malloy JF, Paulus K, Cuthbertson D, Krischer JP: An automated standardized system for managing adverse events in clinical research networks. *Drug Safety* 31(10):807-22, 2008.
- Couluris M, Mayer JL, Freyer DR, Sandler E, Xu P, Krischer JP: The effect of cyproheptadine hydrochloride (peractin) and megestrol acetate (megace) on weight in children with cancer/treatment-related cachexia. *J Pediatr Hematol Oncol*. 30(11):791-7, 2008.
- Richesson RL, Fung KW, Krischer JP. Heterogeneous but "standard" coding systems for adverse events: Issues in achieving interoperability between apples and oranges. *Contemp Clin Trials* 29(5):635-45, 2008.
- TEDDY Study Group: The Environmental Determinants of Diabetes in the Young (TEDDY) Study. *Ann N Y Acad Sci* 1150:1-13, 2008.
- Andrews JE, Patrick TB, Richesson RL, Brown H, Krischer JP: Comparing heterogeneous SNOMED CT coding of clinical research concepts by examining normalized expressions. *J Biomed Inform* 41(6):1062-9, 2008.
- Richesson RL, Lee HS, Cuthbertson D, Lloyd J, Young K, Krischer JP: An automated communication system in a contact registry for persons with rare diseases: scalable tools for identifying and recruiting clinical research participants. *Contemp Clin Trials* 30(1):55-62, 2009.

- **Patents and licenses applied for and/or issued:**

Development of the Moffitt Cancer Network

A notice of disclosure has been filed with the USF office of patents in anticipation of the completion of a patent application.

- **Funding received based on work supported by this award:**

The Data and Technology Coordinating Center for the NIH Rare Disease Network (PI: Jeffrey Krischer, Ph.D.)

The Data Coordinating Center for the Study of the Environmental Determinants of Diabetes in the Young. (PI: Jeffrey Krischer, Ph.D.)

Moffitt Community Clinical Oncology Program Research Base (PI: Jeffrey Krischer, Ph.D.)

Trial to Reduce IDDM in the Genetically at Risk (TRIGR), (PI: Jeffrey Krischer, Ph.D.)

Anti-IL-1 Treatment in New-onset Type 1 Diabetes: Statistical Coordination, (PI: Jeffrey Krischer, Ph.D.)

The TrialNet Data and Technology Coordinating Center (PI: Jeffrey Krischer, Ph.D.)

CONCLUSIONS:

The Advanced Cancer Detection Center has led to publications, presentations and successful grant applications. The funds allocated to the ACDC have supported clinical studies, infrastructure and systems development that have proven to be generalizable and scalable to many other clinical settings. The projects have either been successfully concluded or support for their continuation has been achieved through other funding mechanisms. All projects have been approved for human subjects both at the University of South Florida Institutional Review Board and the clinical setting, as appropriate. The investment in infrastructure has led to cost savings to other federally funded projects and the technology that has been developed has proven to be applicable to a wide range of clinical settings.